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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,109	12/02/2003	Peter Francis Joseph O'Hare	5759-67433-01	4401

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

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01/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/727,109	O'HARE ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 22-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 22-25* is/are rejected.

7)☒ Claim(s) *5,6 and 14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1-31-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 10-31-07.

Claims 1-25 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-31-07 has been entered.

Response to Arguments and Amendments

Applicant's arguments with respect to claims 1-23 have been considered but are moot in view of the new ground(s) of rejection.

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 6, 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 5 is drawn to a polynucleotide comprising modified phosphorothioate linkages. Claim 6 limits these linkages to modified phosphodiester linkages. It is unclear whether claim 5 encompasses phosphorothioate linkages other than internucleotide linkages, as suggested by the subsequent limitation recited in claim 6. Therefore the metes and bounds of claim 5 cannot be determined, or, in the alternative, claim 6 is not further limiting if the phosphorothioate linkages only encompass those which are internucleotide linkages.

Appropriate clarification is required.

Claim 14 depends from claim 1, and claim 1 recites the limitation of covalently bound VP22, yet claim 14 is drawn to non-covalently bound VP22. The metes and bounds of claim 14 cannot be determined.

Appropriate clarification is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to compositions and methods comprising isolated aggregated compositions, wherein the aggregates are between 0.1 and 5 microns, and comprise any isolated polypeptide having the transport function of VP22, and any oligonucleotide, polynucleotide or heterologous polypeptide.

The specification, claims and the art do not adequately describe the distinguishing features or attributes concisely shared by the members of the genera comprising isolated polypeptides having transport function of VP22, which when bound to any oligonucleotide, polynucleotide or heterologous polypeptide, form stable aggregates between 0.1 and 5 microns, and which aggregates disaggregate in cells when exposed to light.

The specification teaches the formation of stable aggregates comprising the polypeptide comprising amino acid residues 159-301 of SEQ ID NO. 12 (which is the carboxy terminus of VP22) in combination with oligonucleotides of 20 nucleotides in length and which comprise fully phosphorothioated internucleotide linkages, at a molar ratio of 2:1, moles VP22: moles oligonucleotide. The genus of aggregates claimed, however, encompasses a vast array of components. The specification, claims and art do not adequately teach a representative number of species for the broad genus claimed. In the reference filed 10-31-07, stable aggregate formation was presumed to be due to the "non-specific charge interactions" (see Normand et al, J. Biol. Chem., Vol. 276, No. 18, at first full paragraph on page 14,044 (2001). The specification does not

teach the formation of stable aggregates using any other polypeptide sharing transport function with VP22. The specification does not teach the formation of stable aggregates using large polynucleotides, or using any heterologous polypeptides. So it is unclear which species of these broad genera of molecules claimed provide for the proper "non-specific charge interactions" required for the formation of stable aggregates.

Concise structural features that could distinguish structures within each genus from others are missing from the disclosure, whereby a representative number of species is particularly described which provides for the function claimed, of forming stable aggregates between 0.1 and 5 microns, and further whereby these stable aggregates disaggregate in cells in the presence of light. For these reasons, the instant disclosure fails to provide adequate written description for the genus of aggregates, and the genera of aggregate components claimed.

Claims 1-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the formation of stable aggregates capable of disaggregating in target cells in the presence of light, which aggregates comprise the polypeptide comprising amino acid residues 159-301 of SEQ ID NO. 12 in combination with an oligonucleotide of 20 nucleotides in length and which oligonucleotide comprises fully phosphorothioated internucleotide linkages, and which composition has a molar ratio of 2:1, moles VP22 polypeptide: moles phosphorothioated oligonucleotide, does not reasonably provide enablement for compositions and methods comprising isolated aggregated compositions, wherein the aggregates are between 0.1 and 5 microns, and

comprise any isolated polypeptide having the transport function of VP22, and any oligonucleotide, polynucleotide or heterologous polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods comprising isolated aggregated compositions, wherein the aggregates are between 0.1 and 5 microns, and comprise any isolated polypeptide having the transport function of VP22, and any oligonucleotide, polynucleotide or heterologous polypeptide.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of VP22 stable aggregate formation. Normand et al (J. Biol. Chem., Vol. 276, No. 18, pages 14,042-14,050 (2001)) and Zavaglia et al (Molecular Therapy, Vol. 8, No. 5, pages 840-844 (2003)) teach the generation of stable aggregates for in vitro and in vivo cell delivery using phosphorothioated antisense oligonucleotides with a length of 20 nucleotides in combination with the carboxy terminus of VP22, amino acids 159-301 of SEQ ID NO. 12, at a specific molar ratio of 2:1, moles VP22 polypeptide: moles phosphorothioated oligonucleotide. Normand et al describe these novel aggregates and admit that the mechanism for aggregate formation and disaggregation in the presence of light upon delivery to cells is unknown: "While we do not yet understand the mechanism

promoting this activity, we have utilized the VP22/ODN particles to deliver candidate ODNs, and demonstrated light dependent activity." (Normand et al at page 15042, last paragraph of the introduction). Furthermore, varying to ratios of the polypeptide and oligonucleotide components led to loss of particle formation (see first full paragraph on page 15,044 of Normand et al). And since stable aggregate formation was presumed to be due to the "non-specific charge interactions" (see Normand et al at first full paragraph on page 14,044), it is unclear what the molecule size and charge requirements are for generating stable aggregates using the broad genus of components claimed, including any heterologous polypeptides, any VP22-like protein and any polynucleotide.

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. The specification does not teach the formation of stable aggregates using any polypeptide, other than amino acids 159-301 of SEQ ID No. 12, that share transport function with VP22. The specification does not teach the formation of stable aggregates using large polynucleotides, or using any heterologous polypeptides. So it is unclear which species of these broad genera of molecules claimed provide for the proper "non-specific charge interactions" required for the formation of stable aggregates.

The specification teaches the formation of stable aggregates comprising the polypeptide comprising amino acid residues 159-301 of SEQ ID NO. 12 (which is the carboxy terminus of VP22) in combination with oligonucleotides of 20 nucleotides in length and which comprise fully phosphorothioated internucleotide linkages, at a molar

ratio of 2:1, moles VP22: moles oligonucleotide. The genus of aggregates claimed, however, encompasses a vast array of components. The specification, claims and art do not adequately teach a representative number of species for the broad genus claimed.

One skilled in the art would not accept on its face the examples provided in the instant disclosure of the ability to produce stable aggregates, using the carboxy terminus of SEQ ID NO. 12 and the fully phosphorothioated 20mer oligonucleotides, as being correlative or representative of the ability to generate stable aggregates using the large genus of molecules claimed in view of the lack of guidance in the specification and the known unpredictability associated with the ability to predict the physical requirements of the aggregate components and the proper molar ratios to generate stable aggregates using this broad array of components.

The breadth of the claims and the quantity of experimentation required. The claims are drawn to compositions and methods comprising isolated aggregated compositions, wherein the aggregates are between 0.1 and 5 microns, and comprise any isolated polypeptide having the transport function of VP22, and any oligonucleotide, polynucleotide or heterologous polypeptide.

The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of the required lengths and physical characteristics of the components, and the appropriate molar ratios required for generating stable aggregates using the broad genus of components claimed. Since the specification fails to provide any particular guidance for the successful generation of

stable aggregates using the broad genus of components claimed, and since determination of the factors required for generating these stable aggregates is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
1-23-08

TC1600

JANE ZARA, PH.D.
PRIMARY EXAMINER